UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	TRANS 1	2472

23535 7590 06/25/2008

MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
06/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,44,46,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 5, 2007 has been entered.

Claims 1-39, 41, 43, 45, 47-55, 59-60 are cancelled.

Claims 40, 42, 44, 46, 56-58, 61 are under consideration.

It is noted that Applicant has filed a request to withdraw finality of Final Office Action, mailed October 9, 2007, on November 5, 2007. In response, Applicant's request is moot as Applicant has filed a Request for Continued Examination (RCE) on November 5, 2007.

Withdrawn Rejections

35 USC § 103

Applicant's arguments, see pages 4-5 of Applicant's response, filed November 5, 2007, with respect to the rejection of claims 40, 61 as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of

Biological Chemistry, 262: 6729-6734 and in view of van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690 have been fully considered and are persuasive. Applicant provides a declaration indicating that the Masters thesis (i.e., the Butler reference) was not available to the public until after August 18, 2000. The rejection of claims 40, 61 has been withdrawn.

Applicant's arguments, see pages 4-5 of Applicant's response, filed November 5, 2007, with respect to claims 40, 42, 44, 46, 56, 58 as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 and in view of Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, have been fully considered and are persuasive. Applicant provides a declaration indicating that the Masters thesis (i.e., the Butler reference) was not available to the public until after August 18, 2000. The rejection of claims 40, 42, 44, 46, 56, 58 has been withdrawn.

Applicant's arguments, see pages 4-5 of Applicant's response, filed November 5, 2007, with respect to claims 40, 57 as being unpatentable over Butler, 1997, Production and Secretion of Recombinant Human Fibrinogen by the Transgenic Murine Mammary Gland, Master of Science Thesis, Blacksburg, VA in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-2734 and in view of Seegers et al., 1950, Blood, 5: 421-433 have been fully considered and are persuasive. Applicant provides a declaration indicating that

the Masters thesis (i.e., the Butler reference) was not available to the public until after August 18, 2000. The rejection of claims 40, 57 has been withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, Seegers et al., 1950, Blood, 5: 421-433, previously cited, van Cott and Velander, 1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, previously cited.

At the time of filing, Meade et al. teach an efficient means of producing large quantities of recombinant protein in the milk of transgenically altered mammals. A DNA sequence coding for a desired protein is operatively linked in an expression system to a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, through a DNA sequence coding for a signal peptide that permits secretion and maturation of the desired protein in the mammary tissue. The presence of the expression system will

permit the female species of the mammal to produce and secrete the recombinant protein product, into or along with its milk. The method permits the lost cost and high level production of the desired proteins (Meade et al., col. 1 under "Disclosure of the Invention" to col. 2). Meade et al. teach that any protein may be produced using their method (Meade et al., col. 3, lines 31-40).

While Meade et al. indicate that the method can be used to make any protein in milk, they do not indicate that recombinant prothrombin is made in milk.

Jorgensen et al. teach that human prothrombin cDNA was expressed in mammalian cells and yielded biologically active, fully gamma-carboxylated prothrombin (Jorgensen et al., abstract). Jorgensen et al. teach that expression vector comprising the coding sequence of human prothrombin was used to express in Chinese Hamster Ovary (CHO) cells and that up to 0.55 ug/ml of prothrombin protein was detected in the culture media (Jorgensen et al., page 6731, 1st col., under “Expression of Recombinant Prothrombin in Chinese Hamster Ovary Cells”).

Given the teachings of Meade et al. and Jorgensen et al., it would have been obvious to one of ordinary skill in the art to take the prothrombin cDNA sequence taught by Jorgensen et al. and use it in the method taught by Meade et al., in order to arrive at a method of making more recombinant prothrombin. It is noted that at the time of filing, an artisan would have wanted to make large amounts of prothombin in order to study its role in blood clotting (Seegers et al., page 421, 2nd parag.).

With regard to the particular embodiment that prothrombin has a completely gamma-carboxylated Gla domain (claim 40), an artisan would have expected at least a fraction of the prothrombin Gla domain to be gamma-carboxylated. According to van Cott and Velander, while transgenic mice were poor at gamma-carboxylating recombinant proteins, transgenic pigs were able to gamma-carboxylate recombinant proteins excreted in milk up to 0.1 g/l/h (van Cott and Velander, page 1686, 2nd col., 3rd parag.).

Thus, the claims are rejected.

Claims 40, 42, 44, 46, 56, and 58 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited.

As indicated above, given the teachings of Meade et al. in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk. While Meade et al. and Jorgensen et al. provide this guidance, they do not teach that prothrombin is post-translationally modified by proteolytic processing.

Le Bonniec et al. teach that prothrombin is activated by bovine factor Xa in the presence of bovine factor Va, phosophlipids, and calcium (Le Bonnic et al., page 13799, 1st col., 2nd parag.). It is noted that activation of prothrombin yields thrombin, the active form of the protein and that thrombin has been studied for its role in blood clotting (e.g. see Le Bonniec et al., page 13796, 1st col., 1st parag.)

Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include a step of adding bovine factor Xa, factor Va, phospholipids, and calcium to prothrombin in order to arrive at thrombin. The art at the time of filing indicates that it is routine in the art to make thrombin from prothrombin and that thrombin made to be studied for its role in blood clotting (e.g. see Le Bonniec).

Thus, the claims are rejected.

Claims 40 and 57 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, in view of Seegers et al., 1950, Blood 5: 421-433, previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited.

As indicated above, given the teachings of Meade et al. in view of Jorgensen et al., an artisan would have arrived at human prothrombin secreted in milk. While Meade et al. and Jorgensen et al. provide this guidance, they do not teach that prothrombin is post-translationally modified by proteolytic processing.

Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate and allowing the mixture to stand at room temperature. After about 5 hours, measurable amounts of thrombin appear (Seegers et al., page 421, 3rd parag., pages 424-425 under "Activation of Prothrombin with Sodium Citrate,"

and Fig. 2). It is noted that at the time of filing, the art teaches that thrombin protein was used in studies to determine its role in blood clotting (Le Bonniec et al., page 13796, 1st col., 1st parag. to 2nd col., 1st parag.).

Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include a step of adding sodium citrate to prothrombin in order to arrive at thrombin. The art at the time of filing indicates that it is routine in the art to make thrombin from prothrombin and that thrombin made to be studied for its role in blood clotting (e.g. see Le Bonniec).

Thus, the claims are rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Art Unit 1632